

-
1. **(Amended)** A method for inhibiting the proliferation, within a population of cells, of T cells containing a nucleic acid encoding a mutated macrolide binding protein (MBP), wherein
- (a) the MBP is selected from an FK506-binding protein (FKBP), cyclophilin, calcineurin, and FKBP:rapamycin associated protein (FRAP);
- (b) the mutated MBP contains an altered amino acid sequence compared with the amino acid sequence of the MBP, and preferentially binds to or forms a complex with a macrolide; and
- (c) the macrolide inhibits proliferation of T cells expressing the mutated MBP, the method comprising contacting the population of cells with the macrolide.
-
4. The method of claim 1, wherein the macrolide binds to or forms a complex with the mutated MBP with a dissociation constant, K_d , at least one order of magnitude less than its K_d for binding to or forming a complex with wild-type MBP.
5. The method of claim 4, wherein the macrolide binds to or forms a complex with the mutated MBP with a dissociation constant, K_d , at least three orders of magnitude less than its K_d for binding to or forming a complex with wild-type MBP.
-
6. **(Amended)** The method of claim 1, wherein the nucleic acid was introduced into the cell *ex vivo* by DNA transfection.
7. **(Amended)** The method of claim 1, wherein the nucleic acid was introduced into the cell *ex vivo* by virus-mediated transduction.
8. **(Amended)** The method of claim 1, wherein the nucleic acid was introduced into the cell *ex vivo* by homologous recombination.
-
9. The method of claim 1, wherein the macrolide is an analog of rapamycin, FK506 or cyclosporin.
-
10. **(Amended)** The method of claim 1, wherein the nucleic acid encodes a FRAP protein, and the macrolide is an analog of rapamycin.
11. **(Amended)** The method of claim 1, wherein the nucleic acid encodes an FK506 binding protein, and the macrolide is an analog of FK506 or rapamycin.

12. (Amended) The method of claim 1, wherein the nucleic acid encodes a calcineurin protein, and the macrolide is an analog of FK506 or cyclosporin.

F3
canon 13. (Amended) The method of claim 1, wherein the nucleic acid encodes a cyclophilin protein, and the macrolide is an analog of cyclosporin.

14. The method of claim 1, wherein the cell is a mammalian cell.

15. The method of claim 1, wherein the cell is a human cell.

F4 16. (Amended) A method for preferentially inhibiting proliferation of genetically engineered T cells in an animal, wherein the genetically engineered T cells include a nucleic acid encoding a mutated macrolide binding protein (MBP) selected from an FK506-binding protein (FKBP), cyclophilin, calcineurin, and FKBP:rapamycin associated protein (FRAP), which method comprises:

- (i) introducing into the animal, genetically engineered T cells which include a nucleic acid encoding the mutated MBP, and
 - (ii) administering to the animal a macrolide which binds to the mutated MBP or forms a complex including the mutated MBP, and which inhibits proliferation of T cells expressing the mutated MBP.
-

18. The method of claim 16, wherein the macrolide binds to or forms a complex with the mutated MBP with a dissociation constant, K_d , at least one order of magnitude less than its K_d for binding to or forming a complex with wild-type MBP.

19. The method of claim 16, wherein the macrolide binds to or forms a complex with the mutated MBP with a dissociation constant, K_d , at least three orders of magnitude less than its K_d for binding to or forming a complex with wild-type MBP.

20. (Amended) The method of claim 16, wherein the nucleic acid was introduced into the cell *ex vivo* by DNA transfection.

F5 21. (Amended) The method of claim 16, wherein the nucleic acid was introduced into the cell *ex vivo* by virus-mediated transduction.

22. (Amended) The method of claim 16, wherein the nucleic acid was introduced into the cell *ex vivo* by homologous recombination.

23. The method of claim 16, wherein the macrolide is an analog of rapamycin, FK506 or cyclosporin.
24. The method of claim 16, wherein the animal is a mammal.
25. The method of claim 24, wherein the animal is a human.
26. The method of claim 16, wherein the introduced T cells are autologous, allogeneic or xenogeneic to the animal.

F6 29. **(Amended)** The method of claim 16, wherein the expression of the mutated nucleic acid is transcriptionally regulated by a T-cell specific transcriptional regulatory sequence.

F7 32. **(Amended)** A nucleic acid encoding a mutated macrolide binding protein (MBP), wherein

(a) the MBP is selected from an FK506-binding protein (FKBP), cyclophilin, calcineurin, and FKBP:rapamycin associated protein (FRAP);

(b) the mutated MBP contains an altered amino acid sequence compared with the amino acid sequence of the MBP, and preferentially binds to or forms a complex with a macrolide; and

(c) the macrolide inhibits proliferation of T cells expressing the mutated MBP.

33. **(Amended)** A kit for preferentially inhibiting proliferation of T cells, comprising

(i) an nucleic acid of claim 32 encoding a mutated MBP, and

(ii) a macrolide which binds to the mutated MBP or forms a complex including the mutated MBP, and which inhibits proliferation of T cells expressing the mutated MBP.

F8 36. **(Amended)** A-population of cells comprising T cells which include a nucleic acid of claim 32.

38. **(Amended)** A method for genetically engineering T cells comprising introducing a nucleic acid of claim 32 into the T cells.

F9 39. **(Amended)** A method for providing an animal which contains T cells containing a nucleic acid encoding a mutated macrolide binding protein (MBP), wherein

9
canu
(a) the MBP is selected from an FK506-binding protein (FKBP), cyclophilin, calcineurin, and FKBP:rapamycin associated protein (FRAP)

(b) the mutated MBP contains an altered amino acid sequence compared with the amino acid sequence of the MBP, and preferentially binds to or forms a complex with a macrolide; and

(c) the macrolide inhibits proliferation of T cells expressing the mutated MBP, the method comprising introducing into said animal the cells of claim 36.

44. (Amended) The nucleic acid of claim 32, which encodes a mutated FKBP or cyclophilin.

Please add the following claim:

45. (New) The method of claim 1, wherein the population of T cells is present within an animal.

The claims presented above incorporate changes as indicated by the marked-up versions below.

1. (Amended) A method for preferentially inhibiting the proliferation, within a population of cells, of T cells which include containing a recombinant gene nucleic acid encoding a mutated macrolide binding protein (MBP), wherein

(a) the MBP is selected from an FK506-binding protein (FKBP), cyclophilin, calcineurin, and FKBP:rapamycin associated protein (FRAP);

(b) the mutated MBP contains an altered amino acid sequence compared with the amino acid sequence of the MBP, and preferentially binds to or forms a complex with a macrolide; and

(c) the macrolide inhibits proliferation of T cells expressing the mutated MBP,

which the method comprises contacting the population of cells with a the macrolide which binds to the mutated MBP or forms a complex including the mutated MBP, and

~~which preferentially inhibits proliferation of T cells expressing the mutated MBP relative to T cells expressing wild-type MBP.~~

6. (Amended) The method of claim 1, wherein the ~~MBP-gene~~ nucleic acid was introduced into the cell *ex vivo* by DNA transfection.
7. (Amended) The method of claim 1, wherein the ~~MBP-gene~~ nucleic acid was introduced into the cell *ex vivo* by virus-mediated transduction.
8. (Amended) The method of claim 1, wherein the ~~MBP-gene~~ nucleic acid was introduced into the cell *ex vivo* by homologous recombination.
10. (Amended) The method of claim 1, wherein the ~~MBP-gene~~ nucleic acid encodes a FRAP protein, and the macrolide is an analog of rapamycin.
11. (Amended) The method of claim 1, wherein the ~~MBP-gene~~ nucleic acid encodes an FK506 binding protein, and the macrolide is an analog of FK506 or rapamycin.
12. (Amended) The method of claim 1, wherein the ~~MBP-gene~~ nucleic acid encodes a calcineurin protein, and the macrolide is an analog of FK506 or cyclosporin.
13. (Amended) The method of claim 1, wherein the ~~MBP-gene~~ nucleic acid encodes a cyclophilin protein, and the macrolide is an analog of cyclosporin.
16. (Amended) A method for preferentially inhibiting proliferation of genetically engineered T cells in an animal, wherein the genetically engineered T cells include a ~~recombinant gene~~ nucleic acid encoding a mutated macrolide binding protein (MBP) selected from an FK506-binding protein (FKBP), cyclophilin, calcineurin, and FKBP:rapamycin associated protein (FRAP), which method comprises:
 - (i) introducing into the animal, genetically engineered T cells which include a ~~recombinant gene~~ nucleic acid encoding the mutated MBP, and
 - (ii) administering to the animal a macrolide which binds to the mutated MBP or forms a complex including the mutated MBP, and which ~~preferentially inhibits proliferation of T cells expressing the mutated MBP relative to T cells expressing wild-type MBP.~~

20. (Amended) The method of claim 16, wherein the ~~MBP-gene~~ nucleic acid was introduced into the cell *ex vivo* by DNA transfection.
21. (Amended) The method of claim 16, wherein the ~~MBP-gene~~ nucleic acid was introduced into the cell *ex vivo* by virus-mediated transduction.
22. (Amended) The method of claim 16, wherein the ~~MBP-gene~~ nucleic acid was introduced into the cell *ex vivo* by homologous recombination.
29. (Amended) The method of claim 16, wherein the expression of the mutated ~~MBP-gene~~ nucleic acid is transcriptionally regulated by a T-cell specific transcriptional regulatory sequence.
32. (Amended) ~~An expression construct~~ nucleic acid encoding a mutated macrolide binding protein (MBP), wherein
- (a) the MBP is selected from an FK506-binding protein (FKBP), cyclophilin, calcineurin, and FKBP:rapamycin associated protein (FRAP);
- (b) wherein the mutated MBP contains an altered amino acid sequence compared with the amino acid sequence of the MBP, and preferentially binds to or forms a complex with a macrolide; and
- (c) the macrolide which preferentially inhibits proliferation of T cells expressing the mutated MBP ~~relative to T cells expressing wild-type MBP~~.
33. (Amended) A kit for preferentially inhibiting proliferation of T cells, comprising
- (i) an ~~expression construct~~ nucleic acid of claim 32 encoding a mutated MBP, and
- (ii) a macrolide which binds to the mutated MBP or forms a complex including the mutated MBP, and which ~~preferentially~~ inhibits proliferation of T cells expressing the mutated MBP ~~relative to T cells expressing wild-type MBP~~.
36. (Amended) ~~An isolated~~ population of cells comprising T cells which include a recombinant gene nucleic acid of claim 32 encoding a mutated macrolide binding protein (MBP) selected from an FK506 binding protein (FKBP), cyclophilin, calcineurin, and FKBP:rapamycin associated protein (FRAP), wherein the mutated MBP binds to or forms a complex with a macrolide, and treatment with the macrolide preferentially

inhibits proliferation of T cells expressing the mutated MBP relative to T cells expressing wild type MBP.

38. (Amended) A method for genetically engineering ~~rendering~~ T cells susceptible to ~~preferential inhibition, which method~~ comprising introducing a nucleic acid of claim 32 into the T cells ~~the expression construct of claim 32~~.
39. (Amended) ~~The~~ A method for providing an animal ~~with preferentially inhibitable T cells,~~ which contains T cells containing a nucleic acid encoding a mutated macrolide binding protein (MBP), wherein
- (a) the MBP is selected from an FK506-binding protein (FKBP), cyclophilin, calcineurin, and FKBP:rapamycin associated protein (FRAP)
- (b) the mutated MBP contains an altered amino acid sequence compared with the amino acid sequence of the MBP, and preferentially binds to or forms a complex with a macrolide; and
- (c) the macrolide inhibits proliferation of T cells expressing the mutated MBP, the method comprising introducing into the said animal ~~preferentially inhibitable T cells prepared by the method of claim 38~~ the cells of claim 36.
44. (Amended) ~~The expression construct~~ nucleic acid of claim 32, which encodes a mutated FKBP or cyclophilin.

REMARKS

Upon entry of the foregoing amendments, claims 1, 4-16, 18-26, 29, 32-33, 36, 38-39, and 44-45 are pending in the application. Claims 1, 6-8, 10-13, 16, 20-22, 29, 32-33, 36, 38-39, and 44 have been amended. Claim 45 has been added. Applicants submit that no new matter has been introduced by the amendments to the claims. The amended claims and new claim 45 are fully supported by the specification as originally filed. Applicants further submit that the amendments are made merely to expedite allowance of claims directed to most commercially